

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor : Dolitzky <i>et al.</i>	Art Unit :1624
Serial No.: 10/649,399	Examiner : Mark L. Berch
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For: CRYSTALLINE SOLID FAMCICLOVIR FORMS I, II, III AND PREPARATION THEREOF

Commissioner for Patents
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DECLARATION UNDER 37 CFR 1.132

S I R:

I,, Ben-Zion Dolitzky, hereby declares:

1. I am one of the co-inventors for the above-identified patent application.
2. I am knowledgeable about the subject matter of the invention and the prior art references relied upon by the Examiner in the Office Action mailed March 18, 2008.
3. I have conducted and/or guided or supervised the conduct of the following experiments.

4. Experiment 1

(corresponding to Harnden et al. (1989), *J. Med. Chem.* 32: 1738-1743; in particular, page 1741, right column, the last 4 lines)

Famciclovir (hereinafter "FMC"), 5 g., were stirred at room temperature in 20 ml methanol. The solid was filtered to obtain an FMC cake, which was dissolved in 50 ml water. The aqueous solution was washed with 15 ml chloroform three times. The organic phases of the

three washes were combined and dried with magnesium sulfate. The solvent was removed from the dried organic phase by evaporation at 50°C under vacuum to obtain a solid FMC residue when the flask was let stand at room temperature.

To determine the solvent content of the solid FMC residue, the solid FMC residue was dissolved in DMSO to form a solution, which was heated at 180°C in a container to release any solvents in the solid residue into the gas atmosphere inside the container. A sample of the gas atmosphere inside the chamber was collected and then analyzed with a gas chromatograph. Chloroform at 898 ppm was detected, but methanol was not detected.

5. Experiment 2

(corresponding to US 6,342,603, Example II-5 in column 8, lines 52-56)

To a 100 ml flask equipped with a magnetic stirrer, 5 g of FMC and 20 ml of ethyl acetate were added. The mixture was stirred at room temperature for 20 minutes. The solvent in the mixture was evaporated under reduced pressure at 50°C to obtain a solid. The solid was recrystallized from 1-butanol by dissolving the solid in 20 ml 1-butanol at reflux to obtain a clear solution, which was cooled to room temperature and a solid began to precipitate after 3 hours. The mixture was stirred at room temperature overnight. The solid was filtered, washed with 1-butanol and dried in a vacuum oven. The dried solid was determined, via powder X-ray diffraction ("PXRD") analysis, to be mainly crystalline FMC Form I with a small amount of another crystalline form of famciclovir which could be FMC monohydrate or crystalline FMC Form II.

6. Experiment 3

(corresponding to US 5,066,805, column 3, the last three lines)

To a 100 ml flask, 5 g of FMC and 20 ml of chloroform:methanol, 95:5 v/v, were added at room temperature until a clear solution was obtained. The solution was evaporated to dryness at 50°C under reduced pressure to obtain a solid. The dried solid was determined, via powder X-ray diffraction analysis, to be crystalline famciclovir Form I

7. Experiment 4

(corresponding to Freer et al. (2000), *Tetrahedron* 56:4589-4595, in particular p. 4595, left column, starting on the 9th line)

To a 100 ml flask, 4 g of FMC and 25 ml of methanol were added achieving complete dissolution. The methanol was evaporated to dryness at 50°C under vacuum. The resulting solid was dissolved in 55 ml of water and FMC was extracted with dichloromethane twice (63 ml and 32 ml). The organic phases were combined, dried with magnesium sulfate and evaporated at 50°C under vacuum. The solid that precipitated was recrystallized from isopropanol. The resulting crystalline solid was filtered and washed with isopropanol. A portion of the wet, washed crystalline solid was analyzed with PXRD and determined to be FMC monohydrate. The other portion of the wet, washed crystalline solid was dried at 50°C in a vacuum oven overnight. The dried crystalline solid was analyzed with PXRD and determined to be mainly crystalline FMC Form I with a small amount of another crystalline form of famciclovir which could be crystalline FMC Form II or FMC monohydrate.

8. Experiment 5

(corresponding to WO 00/06573, Example 11, page 16, lines 5-9)

To a 100 ml flask, 5 g of FMC and 60 ml of tetrahydrofuran were added to obtain a clear solution. The tetrahydrofuran was evaporated at 50°C under reduced pressure. The solid that precipitated was dissolved in 50 ml of water, and was extracted by dichloromethane (23 ml) three times. The organic phases were combined and dried with magnesium sulfate. The dried organic phases were evaporated to dryness at 50°C under reduced pressure. Diethyl ether (30 ml) was added to the solid that had precipitated after evaporation, and the mixture was stirred. The stirred mixture was filtered under vacuum. A portion of the wet solid was subjected to PXRD analysis and determined to be a mixture of FMC monohydrate and crystalline FMC Form I. The other portion of the wet solid was dried in a vacuum oven at 50°C overnight, and then subjected to PXRD analysis which determined the dried solid to be crystalline FMC Form I.

9. Experiment 6

(corresponding to Brand et al. (1999), *Tetrahedron* 55:5239-5252, in particular the paragraph bridging pages 5250 and 5251)

To a 100 ml flask equipped with a magnetic stirrer, 5 g of FMC and 10 ml of a water:acetone (50:50, v/v) mixture were added at room temperature. The mixture was heated to reflux and became a clear solution. The heated solution was cooled to room temperature and stirred overnight at room temperature. Some of the solvent was evaporated and the solution remained clear. The solution was stirred at room temperature for 1.5 hours and a solid began to precipitate. The mixture was stirred overnight. The solid was filtered and washed with 2 ml of a water:acetone (50:50, v/v) mixture. A portion of the wet, washed solid was determined to be FMC monohydrate via a PXRD analysis. The rest of the wet, washed solid was dried in a vacuum oven at 45°C overnight. Based on PXRD analysis, the dried solid was determined to be not crystalline FMC Form I, II or III or FMC monohydrate.

10. All of the above statements made of my own knowledge are true and that all of the statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Signed this 19 day of April 2009 by B. Z. Dolitzky
Ben-Zion DOLITZKY
Declarant